Commentary (Pendergrass/Griffin): What the Physician Needs to Know About Lynch Syndrome: An Update

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Dr. Henry Lynch was one of the first to recognize the existence of hereditary nonpolyposis colorectal cancer (HNPCC). While a relatively small percentage of families have this cancer predisposition syndrome, identification of individuals at risk is now standard of care and includes the potential for the prevention of colorectal cancer. Dr. Lynch and Jane Lynch have written a guide highlighting key points for physicians regarding the diagnosis, surveillance, and management of this disorder. Several aspects of clinical care mentioned in the article are expanded upon here.

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Diagnostic Testing

While mutation analysis by DNA sequencing is the gold standard for diagnosing HNPCC, this is an expensive test for which a patient may need to pay out of pocket. If a patient's family history does not meet Amsterdam criteria, sequencing of the HNPCC genes is not the first step in the testing process. Instead, microsatellite instability testing of colon cancer tissue is considered, often combined with immunohistochemistry (IHC) analysis. Immunohistochemistry staining of tumor tissue detects loss of expression of the genes known to be associated with HNPCC.

Recent studies have analyzed the utility of IHC testing.[1-5] Halvarsson et al[4] reports a sensitivity of 92% and a specificity of 100% for IHC testing of tumor tissue with regard to the MLH1, MSH2, and MSH6 DNA mismatch repair genes. In this study, 128 tumors were tested for microsatellite instability, and 59 of the 128 tumors tested high. Of these 59 tumors with a high level of microsatellite instability, 54 (92%) showed loss of expression by IHC for at least one of the mismatch repair proteins. Of the 28 patients in whom a germ-line mutation was identified, 100% had a corresponding IHC loss of mismatch repair protein expression. The investigators concluded that mismatch repair protein immunostaining facilitates mutation analysis in suspected HNPCC patients because it pinpoints the mutated gene. However, until the genetic background of the highfrequency microsatellite instability tumors with retained mismatch repair protein expression has been clarified, microsatellite instability and IHC testing should be combined in clinical HNPCC analysis.

The Halversson article did not address the role of testing of adenomatous colon polyps. At times, testing of this tissue may be the only option. A study by Loukola et al[6] analyzed the efficacy of microsatellite instability testing on adenomas. This study tested 378 patients, including 11 patients from HNPCC mutation-positive families and 367 patients with sporadic adenomas. From the 11 HNPCC patients, 12 adenomas were tested for microsatellite instability and 6 of the 12 (50%) showed microsatellite instability. Germ-line mutation in MLH1 or MSH2 were identified in five (83%) of the six individuals with microsatellite instability adenomas.

In contrast, in the sporadic adenoma group, only 1 of the 367 adenomas tested (0.3%) showed microsatellite instability. These authors concluded that microsatellite instability analysis in adenomas is likely to be useful in cases where clinical features or family history suggests hereditary predisposition. De Jong et al[7] compared IHC and microsatellite instability testing on adenomas from individuals who had a known germ-line HNPCC gene mutation with those from control individuals undergoing surveillance colonoscopy. In most (65%) of the adenomas from patients with known HNPCC mutations, IHC staining showed no corresponding mismatch repair protein. They recommend IHC staining of large adenomas with high-grade dysplasia in patients under age 60 to identify patients suspected of having HNPCC.
Gynecologic Cancer Screening in HNPCC Families

Women with HNPCC have a lifetime risk of endometrial cancer as high as 60% and a lifetime risk of ovarian cancer of 9%. As the Lynches note, screening is recommended for those at risk. To date, there is no standard screening modality for either of these cancers in HNPCC families and no prospective study documenting effectiveness, but several authors have offered screening recommendations for these at-risk women.

The retrospective study by Rijcken et al[9] reported the results of a 10-year screening experience of 41 women (197 patient-years at risk, median follow-up 5 years) using pelvic examination, transvaginal ultrasound, and CA-125. Of 179 transvaginal ultrasound assessments, 17 were followed by endometrial sampling, yielding 3 premalignant uterine lesions. Of note, an endometrioid adenocarcinoma presenting with bleeding was diagnosed in one woman 8 months after a normal transvaginal ultrasound. No ovarian cancers were identified. They concluded that annual gynecologic screening with transvaginal ultrasound as triage for endometrial sampling remains justified for motivated women. Excluded from the screening study were women from their HNPCC registry who underwent surgery for ovarian or endometrial cancer, which did occur at a significant incidence in this registry population.

Genetic Testing for HNPCC

The Lynches' article illustrates the power of genetic testing to identify a cancer predisposition mutation in a family. Several topics must be discussed with a patient before ordering a genetic test. First, mutation analysis in a family will be most informative if testing is performed on an individual who has an HNPCC-associated cancer. If a mutation is identified in an HNPCC-causing gene in this person, one can conclude that this mutation caused the cancer.

There are several possible outcomes for this testing: (1) If a mutation is detected, other at-risk family members can be tested for this mutation. (2) If no mutation is found in an affected individual, this is inconclusive. HNPCC is not ruled out, as current technology does not detect 100% of mutations in these genes and another gene could be at fault. (3) A variant of uncertain significance may be found. In this situation, an alteration in the DNA of a gene has been identified, but it is unknown whether this will actually affect gene function and influence cancer risk. It is imperative that patients understand that with these latter two results they are still at risk for inherited cancer and should continue to be screened. The only time a "true negative" result can be obtained is when a mutation is identified in an affected family member and another family member tests negative for that specific mutation.

As the Lynches note, consideration of genetic testing may raise concerns regarding genetic discrimination. The Health Insurance Portability and Accountability Act (HIPAA) (1996) prevents group health insurance from denying coverage to new members because of a preexisting medical condition or charging a higher premium to one individual based on that person's medical history. It specifically states that predictive genetic information, including information from genetic testing or family history, cannot be considered a preexisting condition unless the person has already developed the disease. However, it does not provide protection for life or disability insurance, and patients are advised to update these policies prior to genetic testing. Many individual states have laws that provide additional protection.

Conclusions

The Lynches' article reviews HNPCC and, with these additional commentaries, provides a summary of long-standing and new techniques for the diagnosis, surveillance, and management of this hereditary colon cancer syndrome.

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